WYETH-AYERST RESEARCH

April 15, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

SUBJECT: Docket Number: 99D-0121 (Draft Guidance)
"Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System"

Dear Sir/Madam,

This document responds to the Draft Guidance, Docket Number 99D-0121, published in the Federal Register, February 17, 1999 (Volume 64, Number 31). We reviewed the Draft Guidance, and we would like to propose the following suggestions and recommendations. In addition, we bring to your attention the recent USP proposed protocol "Standardization of an *In Vitro* Method of Drug Absorption", published in the March - April 1998 Pharmacopeial Forum. In this proposed protocol, the use of reference standard for method suitability test was also discussed. It would be in the best interest of the industry if the FDA and the USP can provide consistent guidance and recommendations for the standardization of these methods.

Our comments are described as follows under each of the relevant headings of the Draft Guidance.

III. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

A. Solubility

For the determination of the solubility class boundary, the Draft Guidance suggested a volume of 250 ml or less of water over the pH range of 1-8. In order to be consistent with other previously published Guidances for Industry (1, 2), which stated that 250 ml of buffer adjusted between pH 1-8, we recommend that the molarity and the ionic strength of the buffer solutions be specified as published in

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the United States Pharmacopeia (USP). Additionally, the temperature (37°C) for solubility determination will need to be specified so as not to cause any confusion.

Furthermore, in order to simulate more closely the *in vivo* situation, solubility in various simulated fasted and fed gastric and intestinal media, such as those developed by Dr. Dressman, may be more suitable for the solubility class boundary determination. This relevant point was discussed in the August, 1998 AAPS workshop on "Permeability Definitions and Regulatory Standards for Bioequivalence" held in Arlington, VA. Therefore, we suggest that the FDA consider these media as the appropriate media for solubility determinations instead of buffer solutions.

B. Permeability

The Draft Guidance indicated that the permeability class boundary is based on the "extent of absorption" in humans, or other appropriate measurements of the "rate" of mass transfer across intestinal membranes. We would like to clarify that the measured "extent of absorption" should not be confused with the "extent of bioavailability", and that the measurement is not for the "rate" of mass transfer, but rather for the "extent" of mass transfer.

We suggest the addition of "fraction of dose absorbed (fa)" to the "extent of absorption" in this section, or any other appropriate sections when the "extent of absorption" was discussed. Specifically then, a drug substance is considered *highly permeable* when the "extent of absorption" or "fraction of dose absorbed (fa)" in humans is determined to be > 90% of an administered dose.

C. Dissolution

The Draft Guidance suggested not less than 85% of the label amount of the drug substance dissolves within 30 minutes. However, in the previous two Guidances (1, 2), the dissolution time for immediate release solid oral dosage forms was specified to be 15 minutes. Therefore, we recommend a dissolution time of 15 minutes in order to be consistent with the previously published Guidances.

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1. Guidance for Industry, Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes, November, 1995.

2. Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, FDA, CDER, August, 1997.

The Draft Guidance suggested three media for dissolution studies. Based on our experience, we propose that dissolution in pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes is unnecessary for Class I compounds (i.e., high solubility and high permeability). As indicated in the previous Guidances, for high permeability and high solubility drugs, only dissolution in 0.1N HCl medium was required. Again, the molarity and ionic strength of the buffers should follow those as specified in the USP.

The Draft Guidance recommended using USP apparatus I at 100 rpm or apparatus II at 50 rpm. The Guidance should allow flexibility for the industry to use any appropriate dissolution apparatus. Also, the Guidance will need to specify that all dissolution tests for immediate release dosage forms should be conducted at 37 $\pm$ 0.5°C as in the other two Guidances.

Furthermore, the comments on the use of simulated fasted and fed gastric and intestinal media under Section III. A should also be considered here.

IV. METHODOLOGY FOR CLASSIFYING A DRUG

A. Determining Solubility Class

Same comments as in response to Section III. A.

B. Determining Permeability Class

2. Intestinal Permeability Methods

The Draft Guidance proposed using twenty or more selected model drugs to establish the suitability of the method. A total of 20 or more model compounds may be excessive, and we recommend using "10 or more" model compounds. In the USP published proposed protocol for the Caco-2 system, only three reference standards were recommended for a system suitability test. We believe that once a method is properly validated, rank ordering of a list of reference compounds in concordance with the published data would be more meaningful, especially when predicting permeability and fraction of dose absorbed in man.

The Draft Guidance also suggested the use of one or two well characterized model drugs as internal standards to be tested simultaneously along with the

test drug being classified. The internal standards should be compatible (i.e., no physical and chemical interactions) with the test drug being evaluated.

We recommend using one or two standard compounds for routine system testing, without using the term of "internal standard". These compounds will be evaluated in different transwells as in the case of Caco-2 model, or in different animals as in the *in situ* rat perfusion study, at the same time as test compounds are being evaluated. This will minimize potential interactions with test compounds. Due to unforeseen potential interactions, different "internal standards" may need to be selected, and may result in misleading conclusions.

V. REQUESTING A WAIVER OF IN VIVO BA/BE STUDIES

1. The drug substance for which a waiver is being requested should be highly soluble and highly permeable, as defined above.

This clearly applies only to Class I compounds. Therefore, we recommend that "Class I compounds according to the BCS" be added for clarification.

3. The comments are the same as in Section III. A & C., in that the dissolution time is 15 minutes, and only two dissolution media (i.e., 0.1 N HCl or SGF USP without enzymes, and a pH 4.5 buffer) are sufficient. Molarity and ionic strength are to be specified as in the USP. The simulated fasted and fed gastric and intestinal media should be considered.

VI. ADDITIONAL CONSIDERATIONS WHEN PLANNING A REQUEST FOR A WAIVER

A. Instability in the Gastrointestinal Tract

We agree that it is important to document that drug loss from the gastrointestinal tract is due to intestinal membrane permeability and not due to a degradation process. In the *in situ* intestinal perfusion studies in animals, it is our normal practice to demonstrate the stability of a test compound for a minimum of two hours at 37°C in the rat intestinal wash.

However, we disagree with the stability testing of a test compound in gastric and intestinal fluids obtained from human subjects or animals. Currently, this kind of information is not required for any pivotal bioavailability studies of new compounds for NDA filings. If confirmation of GI tract stability is required, we suggest the use of simulated gastric and intestinal fluids with enzymes, if necessary.

B. Evaluation of Excipients

It was suggested that when requesting for biowaiver, a list of equipment used should be provided. We would like to know the rationale for this request.

VII. REGULATORY APPLICATION OF THE BCS

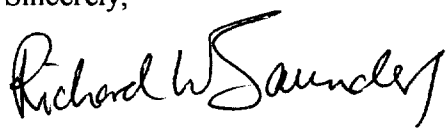
As stated previously in Section III.C, we suggest that the choice of dissolution apparatus (USP I or II) to be deleted from A.1. and B. This will allow flexibility for the industry to select the appropriate dissolution apparatus (though apparatus I/II may be preferred by the FDA).

ATTACHMENT A: SUGGESTED MODEL DRUGS

Polyethylene glycol 400 is suggested as a potential model compound. However, our experience showed that with such a small molecular weight hydrophilic compound, the epithelial permeability would be similar to that of mannitol. Therefore, PEG 4000 would be a better choice as a non-absorbable model compound.

Wyeth-Ayerst Research appreciates the opportunity to participate in the establishment of Guidance for Industry, and looks forward to working with the FDA for the finalization of this Draft Guidance.

Sincerely,



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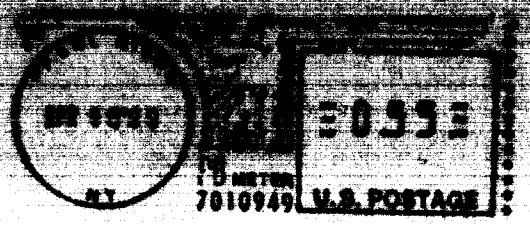

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